Modern Approach to SAH in Intensive Care Unit (ICU)

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Summary

SAH is still a severe pathology carrying a high risk of death or severe neurological morbidity. New diagnostic, monitoring and therapeutic methods are available for the detection and treatment of vasospasm. This includes transcranial Doppler, CT or MRI perfusion scan, protein S100B dosage, cerebral blood flow monitoring at the bedside. Medical treatment of vasospasm relies on increased blood pressure and dobutamine.

Emergency balloon angioplasty or arterial vasodilator infusion is mandatory in case of vasospam-induced ischemic deficit.

Despite several medical advances in the treatment of subarachnoid haemorrhage (SAH) due to aneurysm rupture, particularly interventional neuroradiology, it remains a potentially devastating illness with a high mortality rate. The most important determinant of outcome is neurologic state on arrival in the hospital, assessed with the World Federation of Neurological Surgeons (WFNS) scale (table 1) [1]*. Delayed cerebral ischemia due to cerebral vasospasm and medical complications due to SAH have both a major impact on outcome.*

The cooperative aneurysm study, including 457 patients with SAH, showed that the proportion of deaths from medical complications (23%) was comparable with the proportion of deaths attributed to the direct effects of the initial hemorrhage (19%), rebleeding (22%), and vasospasm (23%) after aneurysmal rupture (2). Thus, the aim of ICU management is to prevent or to limit the consequences of vasospasm and to treat medical complications that can have an adverse effect on the brain.

1. Cerebral Vasospasm

1.1. *Diagnosis of vasospasm in the ICU*

A vasospasm on angiography is found in 30% to 70% of patients after SAH, but is symptomatic in 17% to 40 % of patients. Thus, it is important not only to assess the degree of vessel

Table 1 **Classification of the World Federation of Neurological Surgeons (WFNS)**

Grade	Glasgow Coma Score	Motor deficit	GOS 1-3 at 6 months (%)*
I	15	absent	13
II	13-14	absent	20
III	13-14	present	42
IV	7-12	present or absent	51
V	3-6	present or absent	68

GOS: Glasgow Outcome Score (1-3 : dead, persistent vegetative state or severe disability)

narrowing but also its cerebral haemodynamic consequences. Cerebral angiography is the gold standard to make the diagnosis of vasospasm. However it is an invasive procedure difficult to repeat at frequent times in the same patient. This is the reason why transcranial Doppler ultrasonography (TCD) is very popular in neurosurgical intensive care units. For the middle cerebral artery, compared to cerebral angiography, sensitivity was 67%, specificity was 99%, positive predictive value (PPV) was 97%, and negative predictive value (NPV) was 78% for the diagnosis of vasospasm. For the anterior cerebral artery, sensitivity was 42%, specificity was 76%, PPV was 56%, and NPV was 69%. Thus, TCD may be used to identify patients with a spasm for the middle cerebral artery. For all other arteries, TCD is not enough accurate to predict or rule out vasospasm. It is important to combine the information provided by TCD with other predictive factors of vasospasm, mainly clinical assessment and an index of cerebral blood flow to obtain a "vasospasm probability index"[3].

Computed tomography (CT) perfusion has been validated by comparison with other cerebral blood flow (CBF) measurement techniques. CT perfusion is most reliable when it is used to compare one region of interest (ROI) with those from other ROIs[4]. Assessment of cerebral perfusion on the basis of absolute values of CBF and cerebral blood volume should be made cautiously. But the use of relative values for CT perfusion may be misleading in cases of diffuse vasospasm. Vertebrobasilar vasospasm may also be difficult to assess. CT-perfusion results may also depend on adequate cardiac output or carotid artery disease. With these limitations in mind, CT-perfusion can be used to identify patients at risk of delayed cerebral ischemia. This can lead to alterations in patient management.

Magnetic resonance angiography can show only a narrowing of the major branches of the circle of Willis and is not sensitive enough to detect vasospasm. But perfusion-weighted MRI can provide functional information to detect the tissue at risk for infarction[5]. However, the influence of perfusion MRI on therapeutic management in patients with SAH is still unknown. Whether this imaging technique improves patient outcome or not has still to be demonstrated. Although imaging techniques may help to assess the cerebral hemodynamic consequences of angiographic vasospasm, it would be most useful to have a continuous monitoring of cerebral blood flow at the bedside in the ICU. Thermal diffusion flowmetry (TDF) is a reliable method to detect changes in regional CBF. This method is minimally invasive and uses a microprobe comparable to those used for intracranial pressure monitoring. The focal nature of this monitoring technique needs careful selection of the vascular territory to be monitored. The depth of implantation of the electrode needs to be standardized because CBF in white matter is much lower than in grey matter or mean CBF[6]. Major advantages of the technique are continuous real-time measurements and reactivity to treatments. Case reports have shown the clinical interest for patients with high grade SAH but the technique has still to be validated in a large number of patients.

1.2. *Biological monitoring*

Protein S100 beta (PS100B) is a biomarker of brain damage. Its blood level increases but, due to its short half-life, its dosage has to be repeated frequently. The mean 15-days PS100B had a very high sensitivity and specificity to predict 12-month outcome. Interestingly, PS100B could distinguish between ischemic and non-ischemic vasospasm[7]. Then, it might be possible to initiate aggressive treatment of vasospasm based on PS100B change in case of TCD vasospasm, in order to prevent or to limit severe brain damage. The limitation of PS100B is that its blood level is not related to the volume of brain ischemia, making it a qualitative rather than a quantitative biological marker.

1.3. *Treatment of vasospasm in the ICU*

1.3.1. *Preventive treatment*

Nimodipine is the only demonstrated treatment to reduce the occurrence of severe neurologic deficits due to cerebral arterial spasm[8]. Tirilazad, a molecule of the 21-aminosteroid family, demonstrated inconstant results, particularly in female patients and cannot be recommended. Magnesium is a calcium antagonist and a vasodilator. It reverses cerebral vasospasm and reduces infarct volume after experimental subarachnoid hemorrhage in rats. Recently, magnesium has been studied in a prospective randomized study[9]. Two hundred and eighty three

patients received either magnesium 64 mmol/d or a placebo until 14 days after occlusion of the aneurysm. Magnesium treatment reduced the risk of delayed cerebral ischemia by 34%. After 3 months, the risk reduction for poor outcome was 23%. These promising results have to be validated in a larger phase III trial. In several studies, statins (simvastatine and pravastatine) decreased the incidence of vasospasm. In a small phase II prospective randomized study, pravastatin reduced the incidence of severe vasospasm by 42% and vasospasm related mortality by 83% [10]. In addition, statins improve cerebral autoregulation after SAH [11]. Clazosentan, a selective endothelin A receptor antagonist, has been investigated in two phase II studies. Clazosentan decreased by 50 % the incidence of vasospasm or severe vasospasm [12]. A phase III trial (CONSCIOUS-II study) is underway to demonstrate improved patient outcome.

Prophylactic hypertension, hypervolemia and hemodilution ("triple-H therapy") is considered standard treatment after SAH. However, several prospective studies did not demonstrate any favourable effect on outcome with triple-H therapy [13,14]. On the contrary, cerebral or pulmonary edema have been reported due to massive fluid loading [15]. At present, only treatment of low blood pressure and normovolemia can be recommended.

1.3.2. *Curative treatment*

The aim of the medical treatment is to increase CBF. Vasopressor-induced elevation of mean arterial pressure caused a significant increase of regional cerebral blood flow and brain tissue oxygenation in patients with SAH. Volume expansion resulted in a minimal effect on regional cerebral blood flow and brain tissue oxygenation [16]. Increases in cardiac output with dobutamine without changes in mean blood pressure was equally efficacious to increases in blood pressure with phenylephrine [17]. Whether or not these treatments are additive or synergic is unknown but probably vary from one patient to the other. For most authors, mean arterial pressure (MAP) should be kept between 110-120 mm Hg but some authors recommend increase in MAP up to 150 mm Hg.

The most efficient endovascular treatment of cerebral vasospasm is angioplasty. Its complications include arterial rupture, arterial dissection or thrombo-embolism. The time window between onset of symptoms of focal ischemia and therapeutic angioplasty is only 2 hours. Hence, prophylactic angioplasty has been proposed to limit the consequence of delayed treatment. A prospective multicenter trial has been performed to test this hypothesis in patients with Fisher grade III SAH. Fewer patients tended to develop vasospasm after treatment with prophylactic balloon angioplasty and there was a statistically significantly decreased need for therapeutic angioplasty. But angioplasty did not improve the poor outcome.

Another option is the arterial infusion of vasodilators. Milrinone seems to be safe and effective to dilate spastic cerebral arteries [18]. Due to its limited duration of action, an intravenous infusion is necessary to obtain a sustained effect.

2. Medical complications

Between 40 % and 79 % of patients with SAH develop at least one medical complication during their hospital stay [2,19]. Patients with poor outcome had significantly more medical complications than patients with good outcome. In one study, fever was the most frequent medical complication, followed by anemia, hyperglycemia, and hypertension. Life-threatening complications include cardiac arrythmias, pulmonary edema and sepsis.

Myocardial injury is frequent. In patients with increased troponin blood level on admission, myocardial dyfunction is present in 5 % of cases. This cardiomyopathy is experimentally related to sympathetic activation and catecholamine release during aneurysm bleeding. Some cases of aneurismal SAH tako-tsubo cardiomyopathy have been described [20].

Pulmonary complications are the most common non-neurologic causes of death. Neurogenic pulmonary edema is rare, present in less than 2% of patients. A decreased level of consciousness can promote pulmonary aspiration and infection. One important objective of ICU management is to prevent this complication and to optimize patients oxygenation.

Metabolic complications are both related to SAH and induced by treatments. For example, hypernatremia is highly associated with osmolar therapy for intracranial hypertension and hyperglycemia is associated with artificial nutrition and glucose load.

Conclusion

The aim of modern management of SAH patients in the ICU is to prevent secondary brain injuries. The first objective is the treatment of medical complications especially in patients in a severe clinical condition at admission. From the 4th to the 12th day after aneurysm rupture, the aim is to monitor vasospasm in order to prevent delayed ischemic injury. A combination of techniques, including Doppler, CT or MRI perfusion scan, biomarkers and CBF monitoring in the ICU, is necessary to obtain the best results. Close cooperation with neuroradiologists and neurosurgeons is mandatory throughout the ICU stay.

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